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Clinical paper

Neurological outcomes of patients with history of obstructive sleep apnea after a cardiac arrest☆

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ABSTRACT

Background: Cardiac arrest survivors may have disabilities due to hypoxic brain injury. Patients with obstructive sleep apnea are exposed to intermittent hypoxemia that may lead to ischemic preconditioning. We have hypothesized that patients with obstructive sleep apnea have better neurological outcomes following a cardiac arrest due to preconditioning of the brain.
Methods: We retrospectively analyzed all the survivors of in-hospital cardiac arrest from January 2006 to September 2016. Patients with confirmed or suspected obstructive sleep apnea were selected for further analysis and those without were used as comparison. Primary outcome was neurological functionality on hospital discharge by the Cerebral Performance Category.
Results: A total of 739 patients had cardiac arrest within the study period. The immediate mortality rate was 59% (N = 43) in patients with obstructive sleep apnea and 94% (N = 623) in those without ($p < 0.001$). Approximately 10% (N = 73) were discharged alive and these were selected for further analysis. Patients without obstructive sleep apnea had more frequently "Poor" outcomes compared to those with obstructive sleep apnea (OR 2.91; 95% CI, 1.11–7.66; $p = 0.03$). After adjusting in a multivariate analysis, obstructive sleep apnea was "protective" of "Poor" neurological outcomes: adjusted OR 0.21; 95% CI, 0.06–0.64; $p = 0.01$.
Conclusion: Patients with obstructive sleep apnea had better unadjusted survival rates, and favorable adjusted neurological outcomes at discharge compared to those without obstructive sleep apnea. These results suggest that obstructive sleep apnea patients may tolerate better acute brain ischemia due to preconditioning.

Introduction

In the United States, there are approximately 326,200 out of the hospital cardiac arrest (CA) and 209,000 in-hospital cardiac arrest annually and the majority is due to cardiac disease [1]. The survival rates of CA can improve with a high quality of cardiopulmonary resuscitation (CPR) and special care in the post-CA phase. However, patients who survive may have significant disabilities due to hypoxic brain injury. These include attention deficit, memory problems, depression, and a decreased quality of life [2].

Ischemic preconditioning (IP) is the tolerance tissues develop to the chronic exposure to intermittent hypoxia (IH) [3]. The basics of preconditioning propose an adaptation to low levels of oxygen that would prevent further damage when tissues are exposed to a hypoxic event such as a CA. Patients with obstructive sleep apnea (OSA) are exposed to intermittent hypoxia due to the repetitive apneas making preconditioning a plausible effect. This clinical entity is defined by the apnea hypopnea index of 5 or higher with the association of excessive daytime somnolence [4].

Obstructive sleep apnea is associated with increased risk of stroke, myocardial infarction, and sudden cardiac arrest [5]. The prevalence of OSA among the general population is between 20–30% [6]. Besides the harmful effects of hypoxia in OSA, experimental studies have demonstrated possible cardioprotective and neuroprotective effects of IH [7]. Previous clinical studies have shown a potential protective effect of ischemic preconditioning in the heart [8,9] and the brain [10,11]. White et al. found that patients with myocardial infarction after receiving remote ischemic preconditioning had increased myocardial salvage compared to patients that did not get the treatment [12]. Another study reported better outcomes after a stroke on patients with history of a previous transient ischemic attack [13]. Recent findings suggest that in

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some OSA patients neurogenic preconditioning may occur due to repeated episodes of hypoxemia [14]. Therefore, we hypothesized that patients with underlying OSA will have better neurological outcomes after a CA. To test this hypothesis we sought to compare the neurological outcomes of survivors of CA with previous history of OSA versus those with no history of sleep apnea.

Methods

Study population

The study protocol was approved by the Mayo Clinic Institutional Review Board. We conducted a retrospective chart review of all subjects older than 18 years of age that had suffered an in-hospital cardiac arrest. Patients were selected from the comprehensive institutional Code Blue Dataset from January 2006 to September 2016. The mortality of all patients in the dataset was collected. The survivors of CA were grouped based on the clinical suspicion or confirmed diagnosis of obstructive sleep apnea (OSA) as documented in the clinical chart prior to cardiac arrest. Other independent variables included demographic characteristics and co-morbidities including hypertension, chronic kidney disease, congestive heart failure, coronary artery disease, hyperlipidemia, diabetes mellitus, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, pulmonary fibrosis, and arrhythmia. The severity of illness prior the cardiac arrest was determined using the Acute Physiology and Chronic Health Evaluation II (APACHE) score. Patients with previous neurological disabilities or psychiatric disorders were excluded from the final analysis. In a sensitivity analysis, we excluded patients with other conditions associated with hypoxemia that might induce preconditioning including COPD, pulmonary fibrosis, and pulmonary hypertension. The clinical variables were abstracted from the electronical medical charts (DA) and random chart audits were performed by another physician (JM).

Outcomes

The primary outcome was neurological functionality after the CA based on the Cerebral Performance Category (CPC) score. We defined "Good" outcome as CPC 1–2 and "Poor" outcome as CPC 3–5 [15]. We also calculated the functionality using the Modified Rankin Scale (mRS). We abstracted the clinical variables that were the most distant from the referent physiological values. Secondary outcomes included Glasgow Com Scale (GCS) after CA in-hospital need for mechanical ventilation (MV) and hospital length of stay (LOS).

Statistical analysis

The continuous variables were reported as median values with interquartile ranges (IQR) and the categorical variables were reported as proportions and counts. Univariate analysis was performed to determine the unadjusted associations of independent variables with the neurological outcomes after CA. We used non-parametric, Fisher's and Wilcoxon Rank-Sum tests, as applicable. We then performed multivariate analysis by including all statistically significant clinical variables from the univariate analysis. We also performed a sensitivity analysis by excluding patients with other chronic hypoxemic conditions that might induce preconditioning, as well. The risk estimates are reported as odds ratios (OR) with a 95% confidence interval (CI). Statistical significance was considered at p-value of <0.05. We used JMP 10 Pro statistical software for analysis from SAS (Cary, NC).

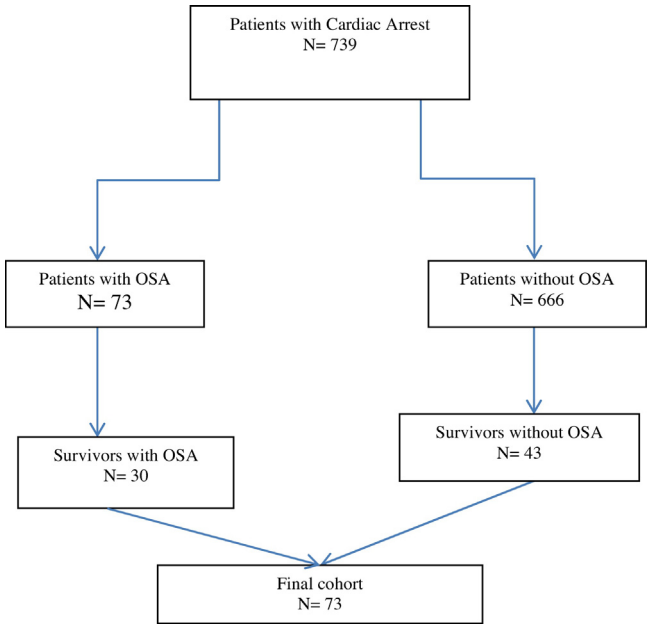

Fig. 1. Study Flow Chart for Patients Who Suffered an In-hospital Cardiac Arrest Between January 2006 and September 2016 at Mayo Clinic, Jacksonville, Florida. OSA = obstructive sleep apnea.

Results

A total of 739 patients had a CA within the study period (Fig. 1). The overall mortality was 90% (N = 666). There were 73 patients (10%) with OSA. The immediate mortality rates after CA were 59% (N = 43) in patients with OSA and 94% (N = 623) in those without OSA ($p < 0.001$). Approximately 10% patients (N = 73) survived to discharge and these were included in the main analysis. Out of these patients, 30 had OSA and 43 did not have OSA. Baseline demographics of this cohort are shown in Table 1.

The median age was 63 years, and the majority was white (92%) and males (63%). Hypertension was the most prevalent comorbidity (68%) followed by hyperlipidemia (49%), and congestive heart failure (44%). Both coronary artery disease and hyperlipidemia were significantly more frequent among patients with OSA (77% and 63% vs 30% and 28%, respectively). The majority of the patients had a cardiovascular event as etiology of the CA (58%), followed by a respiratory event (19%), and a neurological event (12%). One third of the patients presented with pulseless electrical activity (PEA) (36%) followed by ventricular fibrillation (26%), and ventricular tachycardia (16%). A cardiac intervention post CA was seen in 18 patients (25%) and surgery in 11 patients (15%). Infection after CA was seen 35% of the patients and acute kidney injury in 16% of the patients.

Survivors with OSA had lower CPC scores and mRS scores compared to those without OSA ($p = 0.01$ and $p = 0.02$, respectively). Patients with OSA had higher GCS scores following CA compared to those without OSA ($p = 0.03$). There was no significant difference of length of stay and mechanical ventilation duration among patients with OSA and those without (Table 2).

In univariate analysis, only age, APACHE II score, and OSA were significantly associated with neurological outcomes using the CPC score (Table 3). The patients with "Poor" outcomes were older (unadjusted OR 1.04; 95 CI; 1–1.08 $p = 0.04$), and had higher APACHE II score (unadjusted OR 1.07; 1–1.15; $p = 0.03$). The patients without OSA had almost three times the rate of

"Poor" outcomes compared with the patients with OSA; unadjusted OR 2.91; 95 CI, 1.11–7.66, $p = 0.03$. In a multivariate analysis that included age, APACHE II and OSA, as well as the interaction terms for these, all three variables retained significant association